

Osteoarthritis and Cartilage



Dynamic knee loading is related to cartilage defects and tibial plateau bone area in medial knee osteoarthritis

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SUMMARY

Objective: To evaluate the relationship between dynamic mechanical loading, as indicated by external knee adduction moment (KAM) measures during walking, and measures of articular cartilage morphology and subchondral bone size in people with medial knee osteoarthritis (OA).

Design: 180 individuals with radiographic medial tibiofemoral OA participated. Peak KAM and KAM angular impulse were measured by walking gait analysis. Tibial cartilage volume and plateau bone area, and tibiofemoral cartilage defects were determined from magnetic resonance imaging using validated methods.

Results: Both peak KAM (coefficient = 0.42, 95% confidence interval (CI) 0.04–0.79, $P = 0.03$) and KAM impulse (coefficient = 1.79, 95% CI 0.80–2.78, $P < 0.001$) were positively associated with the severity of medial tibiofemoral cartilage defects. KAM impulse was also associated with the prevalence of medial tibiofemoral cartilage defects (odds ratio 4.78, 95% CI 1.10–20.76, $P = 0.04$). Peak KAM ($B = 0.05$, 95% CI 0.01–0.09, $P = 0.02$) and KAM impulse ($B = 0.16$, 95% CI 0.06–0.25, $P = 0.002$) were positively associated with medial:lateral tibial plateau bone area, and KAM impulse was also associated with medial tibial plateau bone area ($B = 133.7$, 95% CI 4.0–263.3, $P = 0.04$). There was no significant association between KAM measures and tibial cartilage volume.

Conclusion: Peak KAM and KAM impulse are associated with cartilage defects and subchondral bone area in patients with medial knee OA, suggesting that increased mechanical loading may play a role in the pathological changes in articular cartilage and subchondral bone that occur with medial knee OA.

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Introduction

Knee osteoarthritis (OA) typically affects the medial tibiofemoral compartment, with a key characteristic of the disease in this form being the loss of medial cartilage with increasing disease severity^{1–4}. In addition to the net loss of medial cartilage, cartilage defects (abnormal intracartilaginous signal or irregularities on the surface or bottom of usually smooth articular cartilage) are an important determinant of osteoarthritic changes^{5,6}, including subsequent loss of articular cartilage volume⁷ and eventual joint replacement⁸. Subchondral bone alterations have also been shown to play a role in the pathogenesis of knee OA⁹. For example, a larger

tibial plateau bone area is associated with more severe cartilage defects and increased risk of joint replacement^{6,10}.

One factor thought to contribute to the loss of articular cartilage in knee OA is increased mechanical load. Employing indirect measures of medial compartment load such as body weight and varus malalignment, previous studies have shown that higher load is associated with greater medial cartilage volume loss^{11–13} and increased presence of medial cartilage defects¹⁴ in knee OA.

A more specific *in vivo* measure of medial compartment load is the external knee adduction moment (KAM); a higher KAM is indicative of higher medial compartment load¹⁵. The KAM has time-varying characteristics over the stance phase of walking gait, typically having two peaks – the first and frequently largest peak in midstance phase and a second peak in terminal stance (Fig. 1). The peak KAM is of particular importance in knee OA as it is related to radiographic disease severity^{16–18} and disease progression¹⁹. More recent data suggest that the knee adduction impulse is also of importance in medial knee OA^{20–22}. This measure, representing the positive area under the KAM vs time curve, incorporates both the

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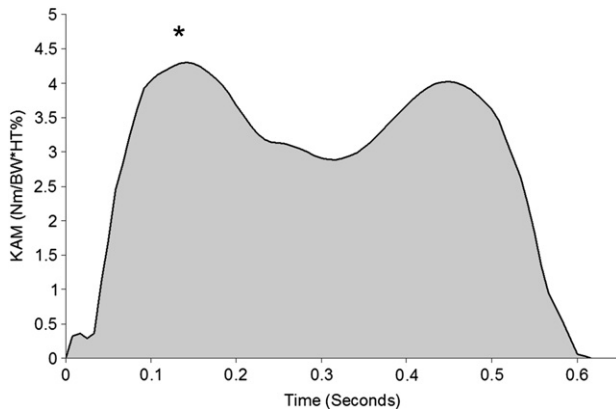


Fig. 1. Typical trace for the KAM during the stance phase of walking for an individual with medial knee OA. Peak KAM (*) and the KAM impulse representing the positive area under the curve (shaded region) are indicated.

average magnitude of the KAM and the duration over which the KAM acts. Thus, it is an indication of total mechanical loading of the medial compartment of the knee during walking²².

Although radiographic progression of medial knee OA has been associated with the peak KAM¹⁹, it is unclear if KAM indices are associated with cartilage specific disease characteristics (cartilage volume and defects) in medial knee OA. Similarly, compartment-specific increases in tibial plateau bone size are associated with more severe radiographic OA²³, yet the relationship between KAM and tibial bone size in the OA population is unknown.

The aim of this study therefore, was to determine the relationship of medial tibiofemoral cartilage morphology (as indicated by tibial cartilage volume and tibiofemoral cartilage defects) and medial tibial plateau bone size with mechanical loading (as indicated by KAM indices). A secondary aim was to determine the relationship of the ratio of medial-to-lateral cartilage volume and bone size with mechanical loading. We hypothesized that higher KAM indices would be related to less cartilage volume, more severe cartilage defects and larger subchondral bone size in the medial tibiofemoral compartment in people with medial knee OA.

Methods

Setting and participants

One hundred and eighty (103 females) participants with radiographic medial tibiofemoral OA were recruited from the community for this cross-sectional study and a randomized controlled trial of lateral wedge insoles²⁴. The measurements included in this study were taken at baseline prior to intervention. Diagnosis of knee OA was based on the American College of Rheumatology classification criteria²⁵. Participants were included if they were aged over 50 years and had knee pain on most days of the previous month (average level > 3 on an 11 point numeric rating scale). Other inclusion criteria were predominance of pain/tenderness over the medial region of the knee and radiographic medial tibiofemoral OA defined as at least grade 1 medial joint space narrowing or grade 1 medial tibial or femoral osteophytes in accordance with the Osteoarthritis Research Society International (OARSI) atlas 4-point scale²⁶. The exclusion criteria were: (i) doubtful or advanced radiographic knee OA (Kellgren & Lawrence (K&L) grades 1 and 4); (ii) predominant patellofemoral joint symptoms based on clinical examination; (iii) knee surgery or intra-articular corticosteroid injection within 6 months; (iv) current or past (within 4 weeks) oral corticosteroid use; (v) systemic arthritic conditions; (vi) history of tibiofemoral/

patellofemoral joint replacement or tibial osteotomy; or (vii) any medication or condition that could affect bone density. If a participant had bilateral disease, the most painful eligible knee was defined as the study knee.

The procedures followed were in accordance with the ethical standards of the University of Melbourne Human Ethics Research Committee and with the Helsinki Declaration of 1975, as revised in 2000. All participants provided written informed consent.

Anthropometric data

Body mass (kg) and height (m) were measured with standard scales and a stadiometer, and body mass index [BMI (kg/m²)] was calculated from these data.

Radiographs

A standardised semiflexed posteroanterior X-ray of the study knee was taken with the participant standing in bare feet. Radiographic severity of tibiofemoral OA was assessed with the K&L system²⁶ by one of two experienced musculoskeletal researchers (KLB/RSH); intra-rater and inter-rater reliabilities in our hands (weighted kappa) are 0.83–0.87 and 0.87, respectively.

Anatomic knee alignment was measured from the X-rays, with high reliability in our hands (intraclass correlation coefficient, ICC = 0.95)²⁷. Alignment measured in this manner is strongly correlated with the mechanical axis taken from a long leg X-ray ($r = 0.75$)²⁸ and avoids the additional cost and radiation associated with a long leg X-ray. A prediction equation was used for conversion to mechanical axis²⁸, where knee alignment of 180° indicates a neutral mechanical axis and lower values indicate varus malalignment.

Gait analysis

A Vicon motion analysis system with eight M2 CMOS cameras operating at 120 Hz (Vicon, Oxford, UK) measured the external KAM of the study knee. The standard Plug-in-Gait lower limb marker set was used. Additional markers were attached to the medial knee and ankle during a single static standing trial to determine the relative positioning of joint centres. Ground reaction forces were measured by two force plates (Advanced Mechanical Technology Inc., Watertown, MA) embedded in the floor at the midpoint of a 10 m walkway at 1080 Hz, in synchrony with the cameras. Participants walked in their usual, low-heeled footwear at their self-selected, normal walking speed. Several practice trials ensured natural gait and valid force plate contact.

Walking speed was calculated across the stance phase of interest from the forward velocity of the pelvis. Joint moments were calculated *via* inverse dynamics (Vicon Plug-In-Gait v1.9). The KAM was normalised for body weight and height²⁹ with the variables of interest being the peak KAM (Nm/BW*HT%) and the positive knee adduction angular impulse (Nm s/BW*HT%) (Fig. 1). Both variables were calculated for each trial and then averaged over five trials. Test–retest reliability of peak KAM and KAM impulse in our laboratory was excellent in a cohort of 11 patients with medial compartment knee OA measured twice 1 week apart; ICC's (3, 5) of 0.98 and 0.96, respectively.

Magnetic resonance imaging (MRI) and knee cartilage and bone measurement

The study knee was imaged in the sagittal plane on one of two 1.5-T whole body magnetic resonance (MR) units using a commercial transmit-receive extremity coil (Philips Medical Systems,

Eindhoven, Netherlands; and GE Medical Systems, USA). The following sequence and parameters were used: a T₁-weighted fat suppressed 3D gradient recall acquisition in the steady state; flip angle 55°; repetition time 58 ms; echo time 12 ms; field of view 16 cm; 60 partitions; 512 × 512 matrix; one acquisition time 11 min 56 s. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 × 0.31 mm (512 × 512 pixels).

Tibial cartilage volume was determined by image processing on an independent workstation using Osiris software (Geneva, Switzerland) as previously described^{30,31}. The measurement was done by two independent trained observers. One observer measured all cartilage data, and the other observer performed cross-checks, i.e., measured one out of five randomly selected participants, in a blinded fashion. The coefficients of variation (CV) for cartilage volume measures were 3.4% for medial tibial and 2.0% for lateral tibial cartilage³². Interobserver reliability assessed in 99 subjects (expressed as ICC) was 0.88 and 0.92 for the medial and lateral tibial cartilage volumes, respectively.

Cartilage defects of the medial tibial and femoral cartilages were graded on the MR images with a classification system previously described^{6,7}. The grading is as follows: grade 0, normal cartilage; grade 1, focal blistering and intracartilaginous low-signal intensity area with an intact surface and bottom; grade 2, irregularities on the surface or bottom and loss of thickness of less than 50%; grade 3, deep ulceration with loss of thickness of more than 50%; grade 4, full-thickness cartilage wear with exposure of subchondral bone. A prevalent cartilage defect was defined as a cartilage defect score of ≥2 at either a tibial or femoral site within the medial compartment. These data were used to define two subgroups, those with and those without medial tibiofemoral cartilage defect prevalence. The measurement was performed by a single trained observer, who measured all images in duplicate on separate occasions. Intra-observer reliability (expressed as ICC) was 0.90 for medial tibiofemoral compartment defect score⁶. The reproducibility for determination of cartilage defects was assessed using the duplicate results, with κ values of 0.92 for the medial tibiofemoral compartment (all $P < 0.001$).

Tibial plateau cross-sectional area was used as a measure of tibial bone size which was determined from images reformatted in the axial plane using Osiris software, as previously described^{9,30}. The measurement was done by two independent trained observers. One observer measured all images, and the other observer performed cross-checks. CVs for the medial and lateral tibial plateau areas were 2.3% and 2.4%, respectively³². Interobserver reliability assessed in 33 participants (expressed as ICC) was 0.95 and 0.86 for the medial and lateral tibial plateau bone areas, respectively.

Statistical analysis

The principle analysis examined the association between mechanical loading variables (peak KAM and KAM impulse) and tibiofemoral cartilage and bone morphology (tibial cartilage volume, tibiofemoral cartilage defects, and tibial plateau bone area). With peak KAM and KAM impulse as the predictors, multiple regression models were constructed with tibial cartilage volume (medial and medial:lateral ratio) and tibial bone area (medial and medial:lateral ratio) as the dependant variables; ordinal regression models were constructed with medial tibiofemoral cartilage defect score in quartiles as the dependant variable; binary logistic regression models were constructed with prevalence of medial tibiofemoral cartilage defects as the dependant variable. All the above regression models were adjusted for age, gender, BMI, MR machine, mechanical axis angle, medial tibial plateau bone area, and walking speed. Analyses of tibial cartilage volume were also

adjusted for K–L grade; analyses of tibiofemoral cartilage defects were also adjusted for tibial cartilage volume. All analyses were performed using SPSS (version 16.0, SPSS, Chicago, IL).

Results

Descriptive characteristics of the study population are presented in Table I.

Both peak KAM and KAM impulse were positively associated with medial tibiofemoral cartilage defect score in univariate analysis and after adjustment for age, gender, BMI, MR machine, mechanical axis angle, walking speed, medial tibial cartilage volume and plateau bone area (Table II). In multivariate analyses, for every unit increase in peak KAM, the expected ordered log odds increased by 0.42 as you move to the next higher category of cartilage defect score. For every unit increase in KAM impulse, the expected ordered log odds increased by 1.79 as you move to the next higher category of cartilage defect score. The R^2 values for the multivariate model were 0.49 and 0.51 for peak KAM and KAM impulse, respectively. KAM impulse was also positively associated with the prevalence of medial tibiofemoral cartilage defects in univariate analysis and after adjusting for the above confounders ($R^2 = 0.21$ for multivariate model; Table II). In univariate analysis and after adjusting for the confounders, neither peak KAM or KAM impulse was associated with medial tibial cartilage volume, or medial:lateral tibial cartilage volume (Table III).

KAM impulse was positively associated with medial tibial bone area and medial:lateral tibial plateau area in univariate analysis and after adjusting for the confounders ($R^2 = 0.65$ and 0.13, respectively for the multivariate models). Peak KAM was positively associated with medial:lateral tibial plateau area ($R^2 = 0.11$) but not medial tibial plateau area after adjusting for confounders (Table IV).

Subgroup analyses on the 167 participants who had knee MRI performed on the Phillips MR machine showed similar results compared with those of the total study population adjusting for MR machine (data not shown).

Discussion

In patients with mild to moderate medial tibiofemoral OA, indices of mechanical loading on the medial compartment during walking were found to be positively associated with the prevalence and severity of tibiofemoral cartilage defects, and tibial plateau bone area in the medial compartment, as well as medial:lateral

Table I
Participant characteristics

	<i>n</i> = 180
Age at MRI (years)	64.1 ± 8.2
Females (<i>n</i> (%))	103 (57)
BMI (kg/m ²)	28.5 ± 4.3
MRI on Phillips scanner	167 (93)
Kellgren–Lawrence grade (<i>n</i> (%))	
2	93 (52)
3	87 (48)
Mechanical axis angle (°)	178.4 ± 2.0
Peak KAM (N m/BW*HT%)	3.77 ± 0.94
Knee adduction angular impulse (N m s/BW*HT%)	1.26 ± 0.37
Walking speed (m/s)	1.26 ± 0.19
Medial tibial cartilage volume (mm ³)	1559 ± 454
Medial:lateral tibial cartilage volume	0.83 ± 0.19
Medial tibiofemoral cartilage defect score	5 (2, 8)
Prevalence of medial tibiofemoral cartilage defects (<i>n</i> (%))	146 (81)
Medial tibial bone area (mm ²)	2388 ± 446
Medial:lateral tibial bone area	1.60 ± 0.21

Values are reported as mean ± standard deviation, median (interquartile range), or number (%).

Table II
Relationship between mechanical loading indices and cartilage defects

	Univariate analysis		Multivariate analysis	
	Coefficient/odds ratio (95% CI)	P value	Coefficient/odds ratio (95% CI)*	P value
Medial tibiofemoral cartilage defect score in quartiles				
Peak KAM (N m/BW*HT%)	0.30 (0.02, 0.59)	0.04	0.42 (0.04, 0.79)	0.03
Knee adduction angular impulse (N m s/BW*HT%)	2.54 (1.72, 3.37)	<0.001	1.79 (0.80, 2.78)	<0.001
Prevalence of medial tibiofemoral cartilage defects†				
Peak KAM (N m/BW*HT%)	1.43 (0.93, 2.23)	0.11	1.51 (0.87, 2.62)	0.14
Knee adduction angular impulse (N m s/BW*HT%)	11.86 (3.25, 43.31)	<0.001	4.78 (1.10, 20.76)	0.04

95% CI = 95% confidence interval.

* Adjusting for age, gender, BMI, MR machine, mechanical axis angle, walking speed, and medial tibial cartilage volume and plateau bone area.

† Odds ratio.

tibial plateau bone area. No significant association was observed for mechanical loading indices and tibial cartilage volume.

Progression of knee OA is widely believed to occur primarily as a consequence of mechanical factors^{33,34}. The mechanism underpinning the relationship between increased medial tibiofemoral loading and progression of cartilage loss in the same compartment is currently unknown. This study demonstrated an independent positive association between KAM measures and medial tibiofemoral cartilage defects in mild to moderate medial knee OA. This is consistent with previous studies implicating higher mechanical loading (peak KAM and KAM impulse) with more severe radiographic disease measured on the K–L scale^{16–18}, and increased radiographic disease progression¹⁹. Our results also suggest that greater mechanical loading is related to the etiopathogenesis of cartilage defects. Compared with peak KAM, KAM impulse showed more evident effects on cartilage defects, being associated with both the severity and prevalence of cartilage defects, while peak KAM was only associated with the severity of cartilage defects. The findings indicate that KAM impulse provides additional information beyond that available from the peak KAM and thus may represent an important gait parameter in OA research¹⁸ that has gone largely unrecognized to date. In contrast, this study did not show significant relationships between KAM measures and tibial cartilage volume, suggesting that cartilage defects may be a more sensitive indicator of cartilaginous change in response to mechanical loading than cartilage volume. Given the established clinical importance of tibial cartilage volume^{10,35} and tibiofemoral cartilage defects^{5–8}, our cartilage defect and volume measures were of the entire medial or lateral compartment, and not limited to the weight-bearing regions of the cartilage. Conceivably cartilage defect and volume metrics that are limited to the weight-bearing region of the cartilage may be more sensitive to mechanical loading effects and future work is recommended to establish this.

There is evidence that KAM measures are related to bone mineral distribution, given their positive associations with medial-to-lateral ratio of proximal tibial bone mineral density and bone mineral content^{22,36,37}. With respect to the effect of KAM on subchondral

bone size, there is only one study showing that peak KAM was positively associated with the size of medial tibial plateau in healthy women without knee OA³⁸. We observed that in patients with knee OA, KAM impulse, but not peak KAM, was positively associated with medial tibial plateau bone area. Taken in tandem with the findings of earlier studies³⁸, it appears that the influence of the KAM upon proximal medial tibial bone size is consistent across healthy and OA knees: higher load is associated with larger proximal medial tibial bone size. Moreover, our data revealed that both peak KAM and KAM impulse were associated with medial-to-lateral ratio of tibial plateau bone area. This may reflect the larger medial tibial bone area we observed with a higher KAM, but may also be indicative of a smaller lateral tibial bone area as a consequence of unloading of the lateral tibiofemoral compartment with a higher KAM^{15,39}.

The KAM during walking gait is a validated proxy for medial compartment knee loading¹⁵. Our study found KAM measures were associated with structural changes of the knee as assessed by cartilage defects and subchondral bone area. Both cartilage defects and subchondral bone expansion have been implicated in the pathogenesis of knee OA. Cartilage defects are predictive of cartilage loss and risk of knee replacement^{7,8}. Subchondral bone expansion is associated with cartilage defects and risk of knee replacement^{6,10}. Our findings support the contention that greater mechanical loading of the medial compartment has a detrimental effect on knee structures and plays a role in the pathogenesis of medial tibiofemoral OA.

Our study has limitations. First, as it was a cross-sectional study, the temporal relationship between mechanical loading and knee cartilage and subchondral bone changes cannot be determined. Longitudinal studies are needed to confirm the causal pathway both for initiation and change in cartilage and bone morphology. Furthermore, the relationship between mechanical loading and cartilage/bone changes may be influenced by other disease characteristics, such as previous joint injury. The interaction with other disease characteristics could also be investigated in future longitudinal studies. Second, although MR imaging sequence and image processing techniques were identical across all participants, two different MR units were employed in this study. This may have

Table III
Relationship between mechanical loading indices and tibial cartilage volume

	Univariate analysis		Multivariate analysis	
	Regression coefficient (95% CI)	P value	Regression coefficient (95% CI)	P value
Medial tibial cartilage volume (mm³)*				
Peak KAM (N m/BW*HT%)	32.6 (–38.7, 103.8)	0.37	57.6 (–17.1, 132.3)	0.13
Knee adduction angular impulse (N m s/BW*HT%)	–25.3 (–204.6, 153.9)	0.78	130.7 (–58.5, 319.9)	0.17
Medial:lateral tibial cartilage volume†				
Peak KAM (N m/BW*HT%)	0.01 (–0.02, 0.04)	0.36	0.01 (–0.03, 0.05)	0.61
Knee adduction angular impulse (N m s/BW*HT%)	–0.03 (–0.11, 0.04)	0.41	–0.01 (–0.10, 0.08)	0.83

95% CI = 95% confidence interval.

* Adjusting for age, gender, BMI, MR machine, Kellgren–Lawrence grade, mechanical axis angle, walking speed, and medial tibial plateau bone area.

† Adjusting for age, gender, BMI, MR machine, Kellgren–Lawrence grade, mechanical axis angle, walking speed, and medial:lateral tibial plateau bone area.

Table IV
Relationship between mechanical loading indices and tibial bone area

	Univariate analysis		Multivariate analysis	
	Regression coefficient (95% CI)	P value	Regression coefficient (95% CI)*	P value
Medial tibial bone area (mm²)				
Peak KAM (N m/BW*HT%)	0.3 (−69.8, 70.5)	0.99	9.3 (−43.1, 61.8)	0.73
Knee adduction angular impulse (N m s/BW*HT%)	291.3 (120.4, 462.1)	0.001	133.7 (4.0, 263.3)	0.04
Medial:lateral tibial bone area				
Peak KAM (N m/BW*HT%)	0.03 (−0.01, 0.06)	0.10	0.05 (0.01, 0.09)	0.02
Knee adduction angular impulse (N m s/BW*HT%)	0.16 (0.08, 0.24)	<0.001	0.16 (0.06, 0.25)	0.002

95% CI = 95% confidence interval.

* Adjusting for age, gender, BMI, MR machine, Kellgren–Lawrence grade, mechanical axis angle, and walking speed.

influenced cartilage and bone area measures. However, we have adjusted for MR machine in all regression analyses and performed subgroup analyses on those who had knee MRI in one MR unit and got similar results. Third, as the study population included only those with mild to moderate radiographic disease, the results cannot necessarily be generalized to those with severe knee OA or those at risk of developing knee OA.

This study demonstrates that peak KAM and KAM impulse are associated with cartilage defects and subchondral bone area in patients with medial knee OA, suggesting that increased mechanical loading may play a role in the pathological changes in articular cartilage and subchondral bone that occur with medial knee OA. Future longitudinal studies are needed to corroborate our findings and investigate the temporal relationship between mechanical loading and knee structure changes.

Author contributions

MC, YW, KB, RH and FC conceived and designed the study; KB, RH, and FC procured the project funding. K-AB recruited and screened the participants; MC, K-AB and BM collected and processed the data. YW performed the statistical analyses. MC and YW drafted the manuscript; KB, RH, BM, K-AB and FC contributed to the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that they have no competing interests.

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